Aus der Klinik und Poliklinik für Radiologie
der Ludwig-Maximilians-Universität München

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Prognostic Value and Role in Response Assessment of Imaging in Advanced Hepatocellular Carcinoma

Exposé zum kumulativen Habilitationsprojekt
zur Erlangung der Venia Legendi
für das Fach Experimentelle Radiologie
der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

vorgelegt von

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aus München
2024

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1. Introduction

Liver cancer was the second leading cause of cancer-related mortality worldwide in 2020, with hepatocellular carcinoma (HCC) comprising most cases [1]. HCC develops due to hepatocarcinogenesis triggered by chronic inflammation of viral hepatitis, alcoholic liver disease, or non-alcoholic steatohepatitis in 90% of the cases [2]. Despite many advancements in locoregional or systemic therapies, HCC has a dismal prognosis with a median survival of around one year at advanced stages [3]. Sorafenib has been the single effective systemic treatment in the first line until the recent approval of immune-checkpoint inhibitor-based combination treatments [4,5]. However, locoregional therapies are also shown to be effective in the early as well as late stages of HCC [6,7]. Selective internal radiation therapy (SIRT) is an intraarterial treatment with the injection of radionuclide Y90 particles into the hepatic artery, which is selectively uptaken by tumor lesions. SIRT has been compared with sorafenib in three randomized controlled trials, alone or combined with sorafenib; however, all three trials failed to show its superiority to sorafenib [8-10]. A meta-analysis of these trials has proven the non-inferiority of SIRT against sorafenib [11]. Additionally, SIRT had significantly fewer adverse events, and quality-of-life maintained longer after SIRT compared to sorafenib [12]. This situation underlines the need for imaging and clinical biomarkers for better patient selection in the era of personalized treatment.

Imaging plays a central role in the management of HCC. In patients with underlying cirrhosis, typical enhancement characteristics in imaging are enough for the diagnosis of HCC and eliminate the need for histopathological evaluation [3]. Additionally, the number of lesions and extension of disease (vascular invasion or extrahepatic disease) on imaging is used for staging of the patients and treatment allocation according to the BCLC scheme [13]. However, patients within the same BCLC class do not benefit from the treatments equally,

and there is a need for additional prognostic features to predict the clinical outcomes of patients. Several other imaging characteristics that reflect tumor biology have been described, such as peritumoral enhancement or hypointensity on hepatobiliary phase images [14]. A number of studies have investigated the prognostic value of these radiological characteristics in early-stage HCC patients. Still, the value of these markers is unknown for patients at advanced stages [14,15].

In addition to detecting tumor nodules, imaging reflects the liver function reserve of the patient. Gadoxetic acid is a hepatocellular specific contrast agent showing selective liver parenchyma uptake, which reaches its highest point approximately 20 min after injection (hepatobiliary phase). The degree of hepatic enhancement decreases as the liver function deteriorates.[16].

Gadoxetic-acid enhanced MRI also allows the detection of lesions at earlier stages of hepatocarcinogenesis with hepatobiliary phase hypointensity without typical enhancement characteristics (non-hypervascular hepatobiliary phase hypointense lesions). Currently, these lesions are not considered in treatment decision-making, although they are shown to be a prognostic factor after potentially curative therapies [17]. Further markers are needed to indicate the treatment of non-hypervascular hepatobiliary phase hypointense lesions.

On the other side, while most of the HCC lesions are hypointense in the hepatobiliary phase, some lesions show gadoxetic acid uptake, which has been shown to correlate with the mutational status of the lesions [18,19]. Therefore, this uptake characteristic could identify sensitivity to some therapies.

Cytokine signaling, including interleukins, plays an intrinsic role in regulating the inflammatory processes leading to hepatocarcinogenesis [20,21]. Various cytokines have been shown to be increased in patients with HCC compared to cirrhotic patients. High baseline interleukin-6 and interleukin-8 values have also been shown to predict treatment response

and overall survival in HCC patients who underwent minimally invasive locoregional therapies [22,23]. A few preclinical studies have shown that IL-6 and IL-8 are related to sorafenib resistance [24,25]; however, the value of these parameters still needs to be defined in clinical cohorts.

Overall survival is the utmost outcome parameter in cancer studies; however, it is diluted with further therapies after progression, especially in trials evaluating first-line therapies. Radiological response parameters have been described to identify patients benefiting from therapies, and secondary outcome parameters like progression-free survival have been used routinely. Unique perfusion characteristics of HCC lesions required specific response criteria based on the enhancement of lesions [26]. Modified RECIST (mRECIST) criteria employ the arterially enhancing portion of the target lesions only in contrast to RECIST. It has been shown to be superior to RECIST in patients undergoing locoregional therapies [27], but its value after systemic therapies is unclear. Furthermore, new criteria for the early identification of patients benefitting from the treatments need to be evaluated.

In the SORAMIC trial, the addition of SIRT to sorafenib has been compared with sorafenib monotherapy in patients with late-stage HCC patients [8]. The primary endpoint of overall survival has been missed, but patient subgroups with benefit from SIRT have been defined [8]. Furthermore, several sub-studies have been planned to identify imaging and clinical prognostic factors to improve patient selection for SIRT.

The first project evaluates the imaging and clinical biomarkers for patients with advanced HCC. BCLC stage-B patients unsuitable for transarterial chemoembolization and BCLC stage-C patients are allocated to systemic treatments. However, BCLC stages of B and C contain a wide range of disease burdens, and these patients do not respond to systemic treatments uniformly. In order to improve treatment allocation as well as patient stratification in randomized trials, additional prognostic markers for advanced-stage HCC patients are

needed. This project has shown that imaging features showing aggressive tumor biology and deteriorated liver function are associated with overall survival and liver decompensation after sorafenib monotherapy or combined with SIRT.

The second project evaluates the correlation between parenchymal enhancement in hepatobiliary phase images and liver function of HCC patients in a multicenter cohort. Several single-center studies have shown that as the liver function deteriorates, the gadoxetic acid uptake of liver parenchyma decreases. However, signal intensity in MRI depends on the scanner and changes with the vendor, magnetic field, or sequence parameters. Until this project, this correlation had not been evaluated in a multicenter-multivendor cohort. This study has shown that although liver enhancement in the hepatobiliary phase correlates with liver function biomarkers, this correlation shows variations between scanner brands.

The third project focuses on risk factors of non-hypervascular hepatobiliary phase hypointense lesions detected in patients with hepatocellular carcinoma. These lesions have been shown to progress into overt HCC during follow-up of cirrhotic patients and lead to earlier recurrence in HCC patients undergoing curative treatments. Yet, there is only scarce available data in the literature on risk factors to identify non-hypervascular hepatobiliary phase hypointense lesions with increased risk, and the effect of systemic treatments on these lesions is unknown. Our study identified T2 hyperintensity, cirrhosis, higher ECOG-PS, and hyperintensity at DWI as risk factors for the progression of non-hypervascular hepatobiliary phase hypointense lesions.

The fourth project evaluates the prognostic value of gadoxetic acid uptake of HCC lesions in patients with advanced HCC who receive sorafenib alone or combined with SIRT. HCC lesions with gadoxetic acid uptake have been shown to predict the ß-catenin mutation status of HCC with a sensitivity of 78.9% and specificity of 81.7%. A preclinical study has identified the β-catenin pathway as the immune escape mechanism by defective recruitment

of dendritic cells and impaired T-cell activity. Mutations in WNT/β- catenin signaling has been shown to be associated with a shorter PFS in patients receiving immune checkpoint inhibitors. Similar to these results, our study has shown that HCC patients with gadoxetic acid uptake in index lesion have significantly shorter overall survival after treatment with sorafenib either as monotherapy or combined with SIRT.

The fifth project evaluates the prognostic value of pretreatment interleukin 6 and 8 levels in patients with advanced HCC treated with sorafenib. Interleukin-6 and 8 are shown to be correlated with sorafenib resistance in preclinical HCC models. However, only a few clinical studies have evaluated the prognostic value of interleukin 6 and 8 in HCC patients, and these studies comprise mostly patients with viral hepatitis. In Western cohorts, the leading etiology of cirrhosis is alcoholic liver disease, unlike the Asian population, and inflammatory signaling pathways differ. In our study, cut-off values of 8.58 pg/mL for interleukin-6 and 57.9 pg/mL for interleukin-8 were independent predictors of overall survival.

In the sixth project, we assessed the correlation between response assessments according to mRECIST and overall survival in patients with advanced HCC who were treated with sorafenib. mRECIST has been defined to overcome the unique challenges in response assessment of HCC patients undergoing locoregional therapies. However, most trials evaluating systemic agents use response assessment according to RECIST as a secondary outcome parameter due to the lack of evidence for mRECIST after systemic therapies. Our study has shown that objective response according to mRECIST is correlated with overall survival after sorafenib treatment.

In the seventh project, the treatment response and progression-free survival after the combination of SIRT and sorafenib have been compared to sorafenib monotherapy in advanced HCC patients. Combination treatment resulted in a significantly higher objective response rate (61.6% vs. 29.8%, $p < 0.001$) and a longer progression-free survival (8.9 vs. 5.4

months, p = 0.022) compared to sorafenib monotherapy. In addition, multivariable analyses confirmed better and more profound tumor control after combination treatment.

2. Relevant academic works

Subproject 1. Osman Öcal, Michael Ingrisch, Muzaffer Reha Ümütlü, Bora Peynircioglu, Christian Loewe, Otto van Delden, Vincent Vandecaveye et al. "Prognostic value of baseline imaging and clinical features in patients with advanced hepatocellular carcinoma." British journal of cancer 126, no. 2 (2022): 211-218.

Patients at increased risk of HCC are biannually screened, yet most HCC patients are diagnosed at advanced stages with a dismal prognosis. Several prognostic clinical factors have been investigated, and patients with low tumor burden and preserved liver function have been identified to have better outcomes. However, except for the lesion diameter and overt vascular invasion, none of the imaging appearances has been utilized in current clinical staging systems [13]. In patients with typical perfusion characteristics, histopathological evaluation is not needed for HCC diagnosis, and biological behavior is not known generally since patients do not undergo biopsy or surgical resection [3]. Some established prognostic factors like the microvascular invasion, which has been shown to correlate with early recurrence after surgery [28], are not used in patients with advanced HCC. Nevertheless, imaging characteristics, like peritumoral enhancement or satellite nodules, are shown to correlate with tumor biology [14,29], but the prognostic value of these imaging features in advanced HCC is not defined. For this, pretreatment CT and MRI images of 376 patients with advanced HCC were evaluated in terms of atypical enhancement, diameter, lesion margin, presence of macrovascular invasion, extrahepatic lesions, biliary dilatation, varices, ascites, pleural effusion, satellite lesions, fat deposition within the lesion, peritumoral enhancement, peritumoral hypointensity on hepatobiliary phase images, diffusion-weighted imaging characteristics, liver and lesion enhancement on hepatobiliary phase images [30]. The presence of ascites, satellite lesions, pleural effusion, atypical HCC lesions, higher ALBI score, LSR < 1.5, presence of peritumoral arterial enhancement, higher bilirubin values, and larger tumor

size were associated with shorter overall survival, while the presence of complete capsule, smooth margin and higher RLE were associated with longer OS. Furthermore, higher ALBI score, presence of satellite lesions, presence of peritumoral hypointensity in the hepatobiliary phase, higher bilirubin values, and ascites were associated with liver decompensation during follow-up, while randomization to the sorafenib arm was associated with a lower rate of liver decompensation.

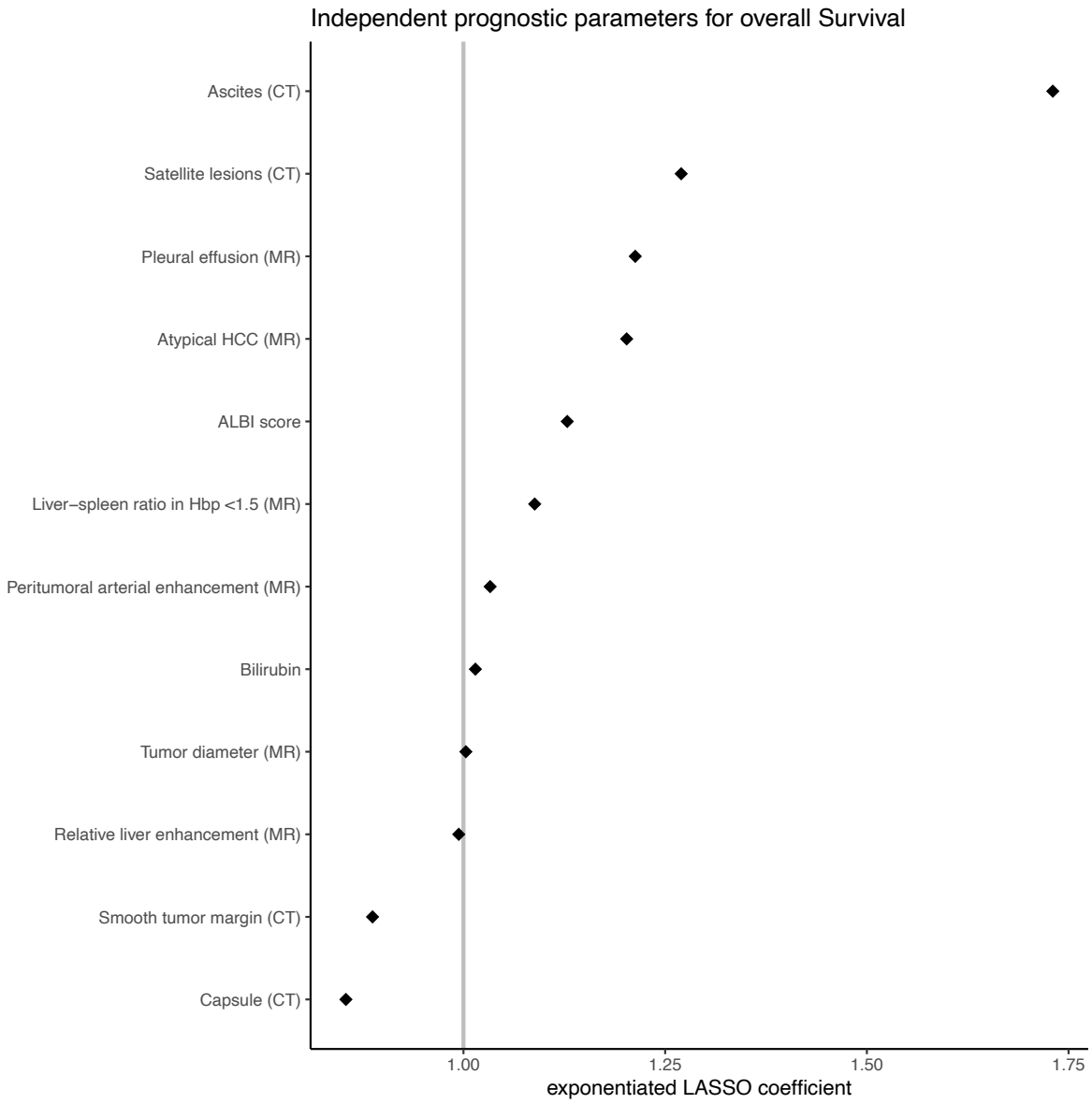

Figure 1. Multivariable Cox proportional hazards regression analysis of variables selected by LASSO for prediction of overall survival.

Subproject 2. Osman Öcal, Bora Peynircioglu, Christian Loewe, Otto van Delden, Vincent Vandecaveye, Bernhard Gebauer, Christoph J. Zech et al. "Correlation of liver enhancement in gadoxetic acid–enhanced MRI with liver functions: A multicenter-multivendor analysis of hepatocellular carcinoma patients from SORAMIC trial." European radiology 32, no. 2 (2022): 1320-1329.

Gadoxetic acid shows an intra- and extravascular compartment distribution in arterial and portal venous phases, similar to other gadolinium-based contrast media. However, it is actively taken up by hepatocytes via organic anion transporting polypeptides (OATP1B1/3) during the transitional (~5 minutes after injection) and hepatobiliary phases (~20 minutes after injection). Liver enhancement in the hepatobiliary phase depends on the concentration of OATPs in the liver, which decreases as the number and function of hepatocytes decrease. However, signal intensity on MRI is a relative parameter that depends on many technical parameters. Several signal intensity-based parameters have been described to overcome these variations by correcting liver enhancement with spleen or muscle intensities on the same phase [16,31]. Our study confirmed the correlation between signal intensity-based assessments (liver-to-spleen ratio) and liver function in a multicenter, multivendor study with a broad variability in scanner brands and field strengths [32]. Additionally, our study showed that despite the significant correlation between LSR and liver function tests, absolute LSR values differ between vendors.

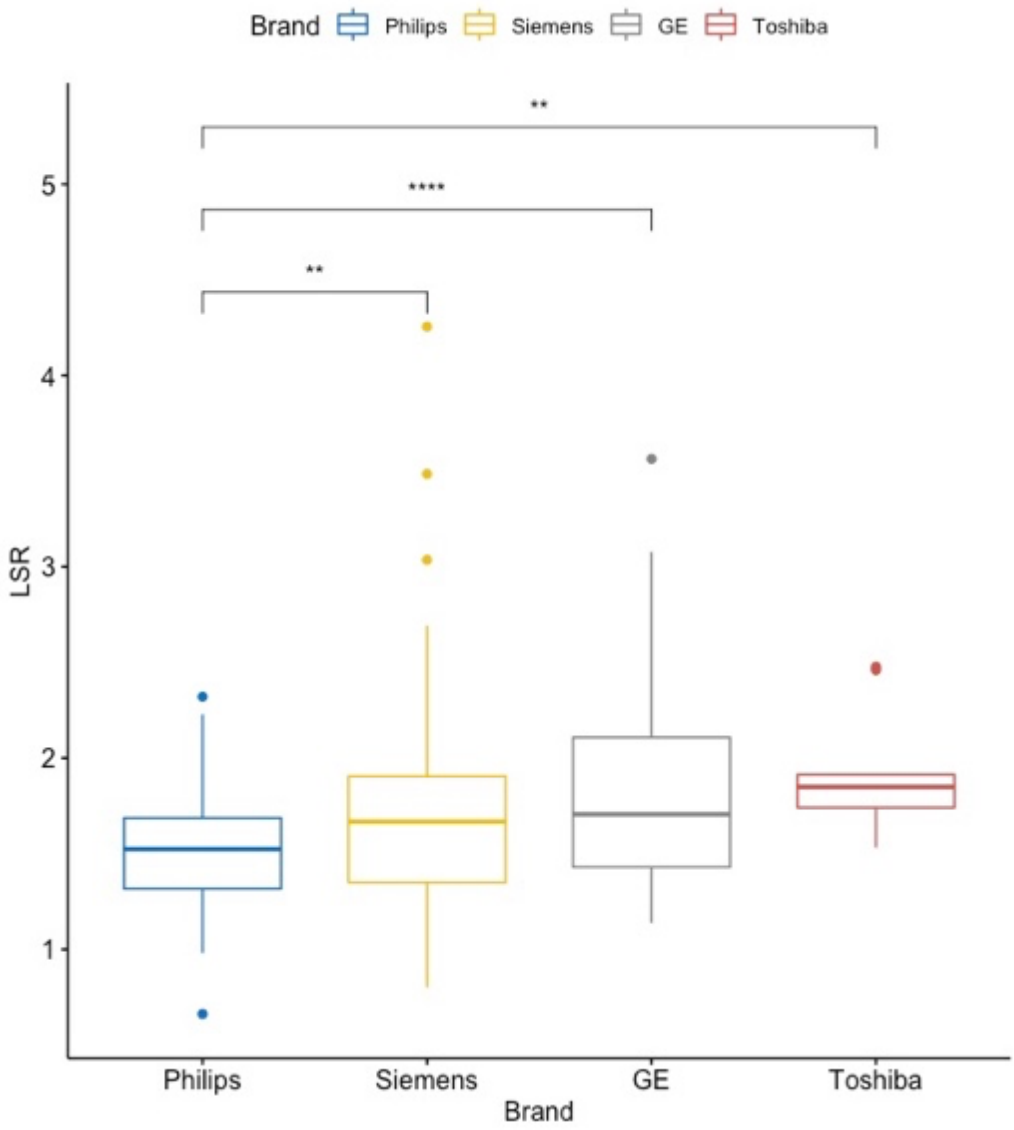

Figure 2 (from [32]). Comparison of LSR between scanner brands. Asterisks show p values for comparison of LSR between each brand and Philips. ** 0.001−0.01, ****< 0.0001

Subproject 3. Osman Öcal, Christoph J. Zech, Matthias P. Fabritius, Christian Loewe, Otto van Delden, Vincent Vandecaveye, Bernhard Gebauer et al. "Non-hypervascular hepatobiliary phase hypointense lesions detected in patients with hepatocellular carcinoma: a post hoc analysis of SORAMIC trial to identify risk factors for progression." European Radiology 33, no. 1 (2023): 493-500.

HCC lesions can be diagnosed non-invasively with excellent specificity (up to 100%) using perfusion criteria [3]. However, arterial hypervascularity and wash-out lack in approximately 20-60% of HCC lesions. Gadoxetic acid-enhanced MRI not only improves HCC detection compared to CT or MRI with other contrast agents but also helps to detect non-hypervascular precursor lesions by hypointensity compared to hepatic parenchyma on the hepatobiliary phase [33]. However, these lesions are not considered in the decision-making process in Western guidelines, despite the fact that they have been shown to correlate with early recurrence after curative therapies [34]. A systematic review has shown that 28.2% of non-hypervascular hepatobiliary phase hypointense lesions progressed into overt HCC during follow-up in patients with cirrhosis [35]. This situation underlines the need for markers to differentiate the lesions with a high-risk for progression. Our study has shown that in patients with HCC, non-hypervascular hepatobiliary phase hypointense lesions with size > 12.6 mm, hypointensity at T1- weighted imaging, hyperintensity at T2-weighted imaging, hyperintensity at DWI images, patients with higher ECOG performance score and cirrhosis are at increased risk for progression during follow-up [36]. And our study has shown that systemic treatment with sorafenib has no influence on the progression of such lesions for the first time.

Teilprojekt 4. Osman Öcal*, Daniel Rössler* (shared first authorship), Antonio Gasbarrini, Thomas Berg, Heinz-Josef Klümpen, Irene Bargellini, Bora Peynircioglu et al. "Gadoxetic acid uptake as a molecular imaging biomarker for sorafenib resistance in patients with hepatocellular carcinoma: a post hoc analysis of the SORAMIC trial." Journal of cancer research and clinical oncology (2021): 1-10.

Most HCC lesions are hypointense on the hepatobiliary phase due to the decrease in OATP concentration as hepatocarcinogenesis. However, some lesions show gadoxetic acid uptake and appear hyperintense in the hepatobiliary phase. Previous studies have shown that this uptake also depends on organic anion transporting polypeptide 1B3 (OATP1B3) as the transporter of gadoxetic acid into HCC lesions [19,37,38]. Furthermore, this uptake has been shown to correlate with the mutational status of HCC lesions, such as the WNT/ß-catenin signaling pathway [39], which leads to resistance to immune checkpoint inhibitors by defective recruitment of dendritic cells and impaired T-cell activity [40]. However, the potential prognostic value of gadoxetic acid uptake is not studied in clinical studies in patients with advanced HCC. This study has evaluated the baseline MRI images of advanced HCC patients who received sorafenib alone or combined with SIRT in terms of gadoxetic acid uptake in index lesions [41]. High gadoxetic acid uptake was significantly associated with shorter overall survival (10.5 vs. 14.0 months, HR, 1.6 [95% CI, 1.1–2.2]; p = 0.005).

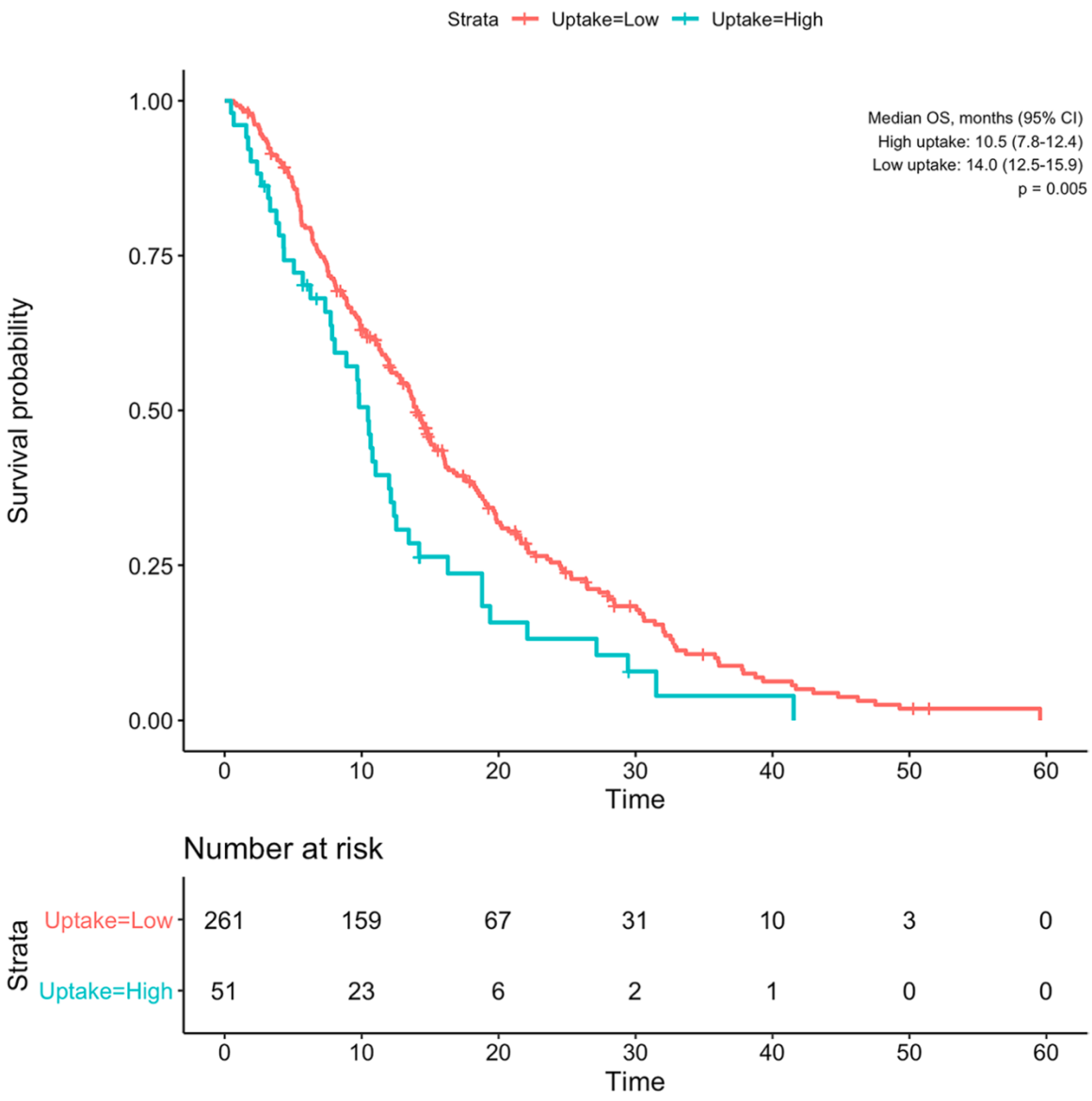

Figure 3. (from [41]) Kaplan–Meier curve showing the overall survival of patients grouped by high and low gadoxetic acid uptake

Subproject 5. Osman Öcal, Kerstin Schütte, Juozas Kupčinskas, Egidijus Morkunas, Gabija Jurkeviciute, Enrico N. de Toni, Najib Ben Khaled et al. "Baseline Interleukin-6 and-8 predict response and survival in patients with advanced hepatocellular carcinoma treated with sorafenib monotherapy: an exploratory post hoc analysis of the SORAMIC trial." Journal of cancer research and clinical oncology (2021): 1-11.

HCC develops approximately in 90% of the patients on the background of chronic inflammation of the liver. HCC represents a classic example of inflammation-linked cancer, and chemically or genetically induced HCC depends on inflammatory signaling. Interleukin-6 is a multifunctional cytokine that orchestrates the hepatic response to inflammation. A preclinical study has shown that suppression of interleukin-6 pathways prevents hepatocarcinogenesis [21]. Also, several preclinical models have shown that interleukin-6/STAT3 signaling contributes to sorafenib resistance in HCC cell lines, and blockage of interleukin-6 increases cytotoxicity of sorafenib [42]. Similarly, interleukin-8 is a macrophage-derived cytokine that induces angiogenesis and recruitment of immunosuppressive cells to the tumor [43]. Inhibition of interleukin-8 pathway has been shown increase sorafenib sensitivity [24]. However, clinical studies evaluating prognostic value of interleukin 6 and 8 are scarce in the literature. Our study has shown that baseline levels of interleukin-6 and interleukin-8 are prognostic markers of overall survival in patients with advanced HCC undergoing sorafenib treatment and identified the cut-off values of 8.58 pg/mL for interleukin-6 and 57.9 pg/mL for interleukin-8 [44]. Furthermore, patients with IL-6 < 8.58 pg/mL had a significantly higher objective response rate than patients with IL-6 higher than cut-off value (46.6% vs. 19.2%, p=0.007). Similarly, IL-8 values lower than the cut-off were also significantly associated with a higher objective response rate (50.0% vs. 17.4%, p=0.011).

Subproject 6. Osman Öcal, Regina Schinner, Kerstin Schütte, Enrico N. De Toni, Christian Loewe, Otto van Delden, Vincent Vandecaveye et al. "Early tumor shrinkage and response assessment according to mRECIST predict overall survival in hepatocellular carcinoma patients under sorafenib." Cancer Imaging 22, no. 1 (2022): 1-13.

Since its efficacy has been proven in two phase III trials, sorafenib had been the single first-line systemic treatment option in advanced HCC over a decade [4,45]. However, despite a significant increase in overall survival in both SHARP and Asia-Pacific trials, there was no significant difference in objective response rate according to RECIST after sorafenib treatment compared to placebo. This situation shows that RECIST is insufficient to capture survival benefit in HCC patients receive systemic treatment. mRECIST has been described to evaluate treatment response after locoregional therapies, which relies on measurement of arterially enhancing part instead of maximum diameter of the lesions [26]. It has been shown to correlate with survival benefit after TACE or SIRT, the value of mRECIST in systemic treatment needs to be defined [46,47]. Besides this, additional markers to detect treatment benefit earlier are needed. Early tumor shrinkage is defined as a reduction in tumor size at the first radiological follow-up evaluation [48]. In this study, the correlation between overall survival and objective response or early tumor shrinkage according to mRECIST has been evaluated using the Mantel-Byar test and landmark analyses to overcome immortal bias [49]. Additionally, time-dependent Cox regression analysis was performed for multivariable analysis. Our results have shown that objective response and early tumor shrinkage by mRECIST in HCC patients receiving sorafenib monotherapy are significantly correlated with treatment outcome and overall survival.

Subproject 7. Osman Öcal, Kerstin Schütte, Christoph J. Zech, Christian Loewe, Otto van Delden, Vincent Vandecaveye, Chris Verslype et al. "Addition of Y-90 radioembolization increases tumor response and local disease control in hepatocellular carcinoma patients receiving sorafenib." European Journal of Nuclear Medicine and Molecular Imaging 49, no. 13 (2022): 4716-4726.

Several retrospective studies have shown that SIRT is an effective and safe locoregional treatment option in HCC patients [50,51]. However, two randomized controlled trials have failed to show the superiority of SIRT over sorafenib in the first-line setting [9,10]. Similarly, the SORAMIC trial has failed to meet the primary outcome of improvement in overall survival after the combination of SIRT and sorafenib compared to sorafenib monotherapy [8]. During the recruitment period of all these three trials, there was no effective second-line treatment option. However, a number of systemic agents have been proven to improve survival in patients who progressed under sorafenib treatment [52-54]. This underlines the importance of secondary outcome parameters like objective response or progression-free survival in trials with first-line treatment setting. In SARAH and SIRveNIB trials comparing SIRT and sorafenib, response assessment had been done according to RECIST 1.1. In our study, the follow-up images of patients recruited in the SORAMIC trial were evaluated centrally according to mRECIST [55]. The objective response rate was significantly higher in patients who received SIRT and sorafenib than patients with sorafenib monotherapy (61.6% [49.5–72.9%] vs. 29.8% [21.2–39.5%], $p < 0.001$). Progression-free survival was also significantly longer in the SIRT and sorafenib arm (8.9 [95% CI, 6.3–9.9] vs. 5.4 [95% CI, 4.1–7.4] months, $p = 0.022$). Furthermore, time-to-progression was significantly longer in patients who received SIRT and sorafenib (10.1 [95% CI, 9.4–18.6] vs. 6.2 [95% CI, 4.9–8.0] months, $p < 0.001$). Recently, two different immune-checkpoint inhibitor-based combinations (atezolizumab-bevacizumab and durvalumab-tremelimumab) have been shown to improve

overall survival in HCC patients compared to sorafenib and became the first-line treatment options. Sorafenib is accepted as the second-line option in patients who progress after these combinations; however, the best treatment sequence is yet to be defined. Our results show that the addition of SIRT to sorafenib in selected cases might improve tumor control in those patients. Also, improvements in the SIRT technique with personalized dosimetry [56], which was not used in all three aforementioned trials, might lead to redefining the role of SIRT in the management of HCC.

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5. Publications

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